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SUMMARY WITH CRITICAL APPRAISAL

Alpha1-Proteinase Inhibitors for the Treatment of Alpha1-Antitrypsin Deficiency: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

Approximately one in 5000 Canadians are affected by severe alpha1-antitrypsin (AAT) deficiency.[1] AAT deficiency is an autosomal codominant condition that results from a homozygous or heterozygous mutation in a serpin family gene on chromosome 14.[2,3] This genetic alteration results in a decrease in production or dysfunction in AAT and most commonly leads to the development of chronic obstructive pulmonary disease (COPD) and emphysema, liver dysfunction, and panniculitis.[2,3] Development of COPD in individuals with AAT deficiency is thought to occur as a result of destruction of lung parenchyma by neutrophil elastases.[2] The activity of these elastases are normally kept in physiologic balance through proteolysis by AAT.[2,4] In cases where AAT is deficient, proteolysis by neutrophil elastase becomes unopposed and leads to the destruction of lung tissue.[2] In individuals with AAT deficiency, smoking increases the rate of decline in lung function.[5] Liver disease in AAT deficiency has been postulated to result from polymerization of aberrant AAT protein in the liver.[2,4] Not all individuals with AAT deficiency will develop COPD or liver disease.[2]

COPD often develops slowly in individuals with AAT deficiency. Management strategies for treating patients with COPD secondary to AAT deficiency are similar to management strategies for treating patients with AAT replete COPD and include pharmacological and non-pharmacological interventions as the mainstay of treatment.[2,6] These management strategies include step-wise addition of both short and long acting bronchodilation with inhaled beta-agonists and anti-cholinergic agents.[2,6] Use of inhaled corticosteroids is also recommended in some patients.[2,6] Smoking cessation is recommended for all patients with COPD.[2,6] Pulmonary rehabilitation is recommended in those patients with decreased exercise tolerance.[6] Supplemental oxygen may be required by some patients.[6] Influenza and pneumococcal vaccines are also recommended.[2,6] Surgical interventions such as lung volume reduction surgery or lung transplantation may be a management option in specific patients with COPD, although their role in AAT deficiency is less clear.[2,6] The most common clinical course of COPD is slowly progressive with worsening dyspnea.[4] Episodes of acute exacerbations can occur which may require oral or intravenous antibiotics and, depending on severity, may necessitate hospitalization.

Disease specific interventions with intravenous alpha1-proteinase inhibitors are available in Canada for individuals with AAT deficiency. Alpha1-proteinase inhibitors are made from purified pooled plasma from human donors. The administration of such agents results in inhibition of the breakdown of AAT and restoration of AAT levels to that required to inhibit elastase activity (>11µmol/L).[3,6] Alpha1-proteinase inhibitors are often referred to as AAT augmentation therapy.[2,3,7,8] A retrospective chart review from the Canadian Alpha-1 Antitrypsin Deficiency Registry published in 2015 found that 290 individuals across Canada had registered over a 151 month period and 42 of these individuals had received AAT augmentation therapy.[8] A CADTH report focusing on clinical evidence for using AAT augmentation therapy in patients with AAT deficiency and forced expiratory volume in one second (FEV1) <30% predicted was published in 2010.[9] The CADTH report found that AAT augmentation therapy slowed decline in lung function in patients with an FEV1 30% to 65% predicted, but the effect in those with an FEV1<30% predicted was not significant.[9]

This report will focus on the clinical effectiveness, cost-effectiveness and evidence based guidelines for the use of AAT augmentation therapy in adult patients with AAT deficiency, regardless of baseline lung function.

Research Questions

1. What is the clinical effectiveness of alpha1-proteinase inhibitors for the treatment of adults with alpha1-antitrypsin deficiency?
2. What is the cost-effectiveness of alpha1-proteinase inhibitors for the treatment of adults with alpha1-antitrypsin deficiency?
3. What are the evidence-based guidelines associated with the treatment of adults with alpha1-antitrypsin deficiency?

Key Findings

Systematic reviews with meta-analysis of randomized controlled trials have found that the mean annual decline in lung density, as measured by CT scan, is significantly less with alpha1-proteinase inhibitors compared to placebo. The rate of decline in FEV1 with alpha1-proteinase inhibitors is variable and contradictory findings are reported in the literature from studies with different methodology. Randomized controlled trials have failed to find a significant difference in FEV1, while observational studies have demonstrated a slower decline with the use of alpha1-proteinase inhibitors. The effect of alpha1-proteinase inhibitors on rates of exacerbations is contradictory in the literature. Alpha1-proteinase inhibitors have not been demonstrated to lead to an improvement in patient quality of life compared to placebo.

Evidence-based guidelines recommend that alpha1-proteinase inhibitors may be considered in non-smokers or previous smokers with alpha1-antitrypsin deficiency with COPD who are receiving optimal pharmacological and non-pharmacological management. The degree of airflow obstruction in which alpha1-proteinase inhibitors are recommended varies across guidelines.

No studies met the inclusion criteria to address the cost effectiveness of alpha1-proteinase inhibitors for the treatment of adults with alpha1-antitrypsin deficiency.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 23, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with alpha1-antitrypsin deficiency
Intervention	Alpha1-proteinase inhibitors (Prolastin-C and Zemaira)
Comparator	Q1-2: Standard of care; Placebo; No treatment Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., but not limited to, FEV_1, CT lung density, functional residual capacity, exacerbations, upper respiratory tract infections, lung or liver transplant, patient reported outcomes [e.g., quality of life], patient satisfaction) Q2: Cost effectiveness (e.g., cost per QALY increase, cost per hospitalization/exacerbation avoided) Q3: Guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Economic Evaluations, Evidence-based Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were included as one of the studies in a systematic review (SR), or were published prior to 2010. Guidelines were excluded if they were not evidence based or did not report methods of data acquisition.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised using AMSTAR[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 345 citations were identified in the literature search. Following screening of titles and abstracts, 314 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 30 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Two SRs addressed the clinical effectiveness of AAT augmentation therapy with alpha-1 proteinase inhibitors[12,13] and four evidence based guidelines provided recommendations on the use of AAT augmentation therapy in the management of individuals with AAT

deficiency.[1,5,14,15] Data from an open label extension (OLE) of one RCT that was included in both SRs was also reported.[16] There were no studies that met the inclusion criteria to address cost-effectiveness of AAT augmentation therapy with alpha-1 proteinase inhibitors.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

A summary of the characteristics of the included literature are briefly described below and detailed in Appendix 2.

Study Design

Two SRs evaluated the clinical effectiveness of AAT augmentation therapy in individuals with AAT deficiency.[12,13] One of the SRs included both RCT and observational studies[12] and the other included only RCTs.[13] One SR[12] included 52 studies, 26 of which evaluated AAT augmentation therapy. Three of these studies were RCTs, and the remainder were observational studies.[12] The other SR included 3 RCTs.[13] Both of the SRs included the same 3 RCTs, one of which was the RAPID trial.[17] Data from the OLE phase of the RAPID trial was published separately.[16] The SRs were published in 2017[12] and 2016.[13] Four evidence based guidelines addressed treatment of adults with AAT deficiency.[1,5,14,15] All four used SR methodology to obtain the evidence for the guidelines. One reported that GRADE methodology was also followed during guideline development.[14] The guidelines were published in 2012,[1] 2015,[14] 2016,[5] and 2017.[15]

Country of Origin

The SRs were conducted by authors in the United Kingdom[12] and Denmark.[13] Guidelines were published by organizations in the United States of America,[5] Spain[14] and Canada.[1] One guideline was worldwide and included authors from many different countries.[15]

Patient Population

The patient population in the three RCTs that were included in both SRs were previous or never smokers with severe AAT deficiency (serum levels <11µmol/L) who had moderate air flow obstruction (FEV1=30% to 80% predicted).[12,13] These RCTs compared AAT augmentation therapy with placebo. One SR reported that the RCTs included a total of 320 participants[12] and the other SR reported a total of 330 participants.[13] The reason for this difference is unclear. The mean FEV1 in the intervention arms ranged from 46 to 50% and 46% to 47% in the control arms.[12] Mean age in the intervention arms was 54 to 55 years and 52 to 55 years in the control arms. Males represented 52% to 66% of the included population in the intervention arms and 41% to 58% of the population in the control arms.[12] The RAPID-OLE enrolled 141 of the 180 participants who initially were part of the 2-year RAPID trial and followed them for another 24 months.[16] The demographics in RAPID and RAPID-OLE were similar. The observational studies in one SR[12] included both controlled (6 studies with 2610 participants) and uncontrolled studies (12 studies with 2526 participants). The patient populations in these studies were small with wide variability in characteristics. The guidelines[1,5,14,15] were focused on including evidence for AAT augmentation therapy in individuals with AAT deficiency. Two of the guidelines specifically stated that application was intended for individuals who had evidence of air flow obstruction.[1,14]

Interventions and Comparators

Both SRs included three RCTs that compared AAT augmentation therapy with placebo.[12,13] They did not report whether patients in the included trials were receiving concomitant treatment with other therapies. The RAPID-OLE compared individuals who received four years of AAT augmentation (early-start group, n=76) to those who received two years of AAT augmentation therapy (delayed-start group, n=64).[16] All participants in the RAPID-OLE trial received AAT augmentation therapy with Zemaira.[16] Six observational studies included in one SR also used no augmentation therapy as a comparator, while 12 were uncontrolled studies.[12] All four guidelines evaluated the use of AAT augmentation therapy.[1,5,14,15]

Outcomes

Outcomes of interest were similar across both SRs[12,13] and one of the guidelines[1]. These outcomes included lung density measured by CT scan, FEV1, diffusing capacity for carbon monoxide (DLCO), quality of life, exacerbations, and mortality. One of the guidelines was also reported dyspnea, exercise capacity and activity, as well as health care use.[1] The other three guidelines did not state the outcomes of interest.[5,14,15]

Follow-up Period

One SR included studies that followed patients for up to 2 to 3 years[13] and the other SR included studies that followed patients for up to 7 years.[12] RAPID-OLE followed participants for two additional years after the completion of the two-year RAPID trial.[16]

Summary of Critical Appraisal

Strengths and limitations of the included studies and guidelines are provided in Appendix 3.

Overall, both included SRs[12,13] were of moderate quality as assessed by the AMSTAR tool.[10] Both SRs reported an *a priori* design and completed a comprehensive literature search including searches of the grey literature.[12,13] Study selection was completed independently and in duplicate in both SRs.[12,13] Both SRs reported a list of included studies; however, only one SR reported a comprehensive list of baseline study characteristics.[12] Neither SR provided a list of excluded studies. In one of the SRs outcome data was extracted independently and in duplicate.[13] In the other SR, data extraction was completed by one reviewer and checked by a second.[12] Risk of bias was assessed in both SRs. In one of the SRs quality appraisal was completed independently and in duplicate.[13] In the other SR, risk of bias was completed by one reviewer and checked by a second.[12] Where meta-analysis was undertaken, both SRs used appropriate statistical techniques. One of the SRs[13] described a plan to explore publication bias but stated that they were unable to complete this plan as there were too few included studies. The other SR[12] did not explore the presence of publication bias. Quality of the included studies was clearly considered when formulating conclusions in one of the SR.[13] Two authors reported receiving grant funding from the Alpha-1 Foundation.[12] The authors of the other SR reported that they had no conflicts of interest.[13] Two of the RCTs included in both of the SRs[12,13] were funded by the manufacturers of the AAT augmentation therapy. The third RCT was publically funded. One of the SRs[13] reported a detailed risk of bias assessment of the RAPID trial,[17] which was the original study for the included open label extension data.[16] Authors reported a high risk of reporting bias as many secondary outcomes were not reported.[13] SR authors also commented that the RAPID trial was sponsored by the pharmaceutical industry and the sponsor was involved in both data collection, analysis and report writing.[13] The risk of selection, performance, detection and attrition bias were unclear.[13] Randomization was

completed using a computerized pseudo random number generator, which SR authors reported as a low risk of bias.[13] Conversely, the other SR reported the overall risk of bias of the RAPID trial as low.[12] Few details on how authors arrived at this interpretation were provided.[12]

Overall, the quality of the four included evidence based guidelines were good,[1,15] and moderate,[5,14] as assessed by the AGREE II tool. All four evidence based guidelines had clearly specified objectives and target patient populations and used SR methodology to obtain the evidenced used to support guideline development.[1,5,14,15] One guideline reported that only published literature was included.[15] Criteria for selecting evidence was not clearly described in any of the guidelines. Three of the four guidelines described the target audience for use.[1,5,15] All four guidelines described methods used, made links between evidence and recommendations, and made recommendations that were clearly described and easily identifiable. Guideline development groups were multidisciplinary in one guideline[1] and composed mainly of physicians in two others.[5,15] In one of the guidelines, it was unclear which professional group the guideline authors belonged.[14] Limitations and potential biases of included evidence were discussed in three of the guidelines.[1,14,15] Two of the guidelines underwent external peer review.[1,15] A process for external review was not described in two cases.[5,14] None of the guidelines clearly discussed the values and preferences of patients, although one guideline was supported by a patient organization[5] and another guideline stated that patient preferences were considered.[15] One of the included guidelines clearly described alternative management options.[15] Two of the guidelines[1,15] describe facilitators and barriers to application, developed tools to assist with guideline translation into practice and had a procedure in place for regularly updating the guidelines. References to cost were made in the guidelines but none included or undertook a formal pharmacoeconomic analysis. Funding from pharmaceutical companies either supported the organization that developed the guidelines[1] or guideline authors had declared having received funding from pharmaceutical companies.[5,14] One of the guidelines received funding support in the form of travel and meeting expenses from a patient organization.[5] One guideline did not report any sources of funding.[15]

Summary of Findings

The overall findings are summarized below and details are available in Appendix 4.

What is the clinical effectiveness of alpha1-proteinase inhibitors for the treatment of adults with alpha1-antitrypsin deficiency?

FEV1

The mean difference in FEV1% predicted decline was not significantly different between AAT augmentation therapy compared to placebo (P=0.20) in one systematic review, based on RCT data.[12] Change in FEV1 was reported in one systematic review and was also not significantly different between AAT augmentation therapy and placebo (P=0.12).[13] No significant differences in pulmonary function tests were found between the early and delayed start groups in the RAPID-OLE.[16] Decline of FEV1 was reported in four observational controlled studies that were included in one SR.[12] Overall, these studies found that AAT augmentation therapy significantly decreased the rate of decline in FEV1. Participants with FEV1>65% had a significant reduction in FEV1 decline with AAT augmentation therapy in two studies, although a third study did not find any benefit.

Participants with an FEV1 between 35% to 49% receiving AAT augmentation therapy also had a significantly lower decline in FEV1 compared to placebo (P=0.03).[12]
The SR reported that individuals with FEV1<30% did not benefit from a reduction in FEV1 with AAT augmentation therapy, although this was not consistently seen across all the observational studies.[12] A registry study included in one SR found that the rate of FEV1 decline in individuals receiving AAT augmentation therapy was significantly slower in individuals with FEV1<30% compared to those with an FEV1 30-65% (P=0.0008).[12]

Lung Density measured by CT scan

In both SRs, the mean annual decline in lung density was significantly less on AAT augmentation therapy compared to placebo (P=0.002).[12,13] Between 24 to 48 months follow-up, the RAPID-OLE did not find a significant difference in the annual rate of decline in lung density (as measured by CT scan) between the early-start group and the delayed-start group, mean difference -0.37g/L (95% confidence interval [CI] -1.16 to 0.42, P=0.82).[16] The rate of loss in lung density was significantly slower in the delayed-start group in the 24 months after initiating AAT augmentation therapy compared to the 24 months during placebo administration, mean difference 0.52 (95%CI 0.22 to 0.83, P=0.0008).[16]

Exacerbations

One SR found that annual patient-reported episodes of exacerbation were significantly lower in the placebo group compared to those who received AAT augmentation therapy (P=0.02).[12] The other SR[13] did not undertake meta-analysis of this outcome due to skewed distribution of data, but stated that both the RCTs reporting this outcome found that numerically more exacerbations occurred in the AAT augmentation group compared to placebo. An observational controlled study included in one SR[12] found that participants experienced significantly fewer exacerbations after receiving AAT augmentation therapy than before (P<0.01).[12]

Quality of Life

Health status, measured by the St Georges Respiratory Questionnaire (SGRQ), was not found to be significantly different between AAT augmentation therapy and placebo in one SR.[12] The other SR[13] did not undertake a meta-analysis of this outcome because conflicting data were available from two different sources with respect to one RCT.[13] No significant difference in SGRQ was found between the early and delayed start groups in the RAPID-OLE.[16] SGRQ is used to determine quality of life in patients with obstructive airway disease. Possible scores range from 0 to 100, with higher scores being associated with worse quality of life. The minimal clinically important difference on this score is a 4-point change.[18]

DLCO

Difference in DLCO was not significantly different between AAT augmentation therapy and placebo in either of the SR.[12,13]

Mortality

One RCT that was included in both SRs reported mortality. One individual who received AAT augmentation therapy died compared to three individuals who received placebo (P=NR). Mortality from an observational controlled study included in one SR[12] found that in participants with an FEV1<50% who never received AAT augmentation therapy mortality was higher compared to those who received it sometimes or always (P<0.001).[12] Mortality was not reported for other subgroups of participants.

Upper Respiratory Tract Infections

Neither SR reported data on respiratory tract infections.

What is the cost-effectiveness of alpha1-proteinase inhibitors for the treatment of adults with alpha1-antitrypsin deficiency?

There were no studies that met the inclusion criteria to address this question.

What are the evidence-based guidelines associated with the treatment of adults with alpha1-antitrypsin deficiency?

Global Initiative for Chronic Obstructive Lung Disease (GOLD),[15] Canadian Thoracic Society (CTS),[1] and Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)[14] guidelines all state that AAT augmentation therapy may be considered in non-smokers or previous smokers with AAT deficiency with COPD who are receiving optimal pharmacological and non-pharmacological management. CTS defined optimal therapy as including comprehensive case management and pulmonary rehabilitation.[1] The FEV1 parameters for recommending AAT augmentation therapy differ slightly across these three guidelines. CTS[1] recommends that AAT augmentation therapy be considered in individuals with FEV1 between 25% to 80% predicted, SEPAR[14] recommends augmentation therapy in those with FEV1<80% predicted, and GOLD[15] states that AAT augmentation may be most suitable for individuals with an FEV1 between 35% and 60% predicted. The COPD Foundation guidelines recommend AAT augmentation therapy in AAT deficient individuals with FEV1≤65% predicted.[5] The COPD Foundation guidelines recommend that in individuals with an FEV1>65% predicted, a discussion regarding the potential benefits and costs should be undertaken with the patient prior to initiation of treatment.[5] The COPD Foundation also recommends AAT augmentation therapy for management of individuals with AAT deficiency and necrotizing panniculitis.[5] The COPD Foundation does not recommend AAT augmentation therapy for individuals who continue to smoke, those with bronchiectasis without evidence of airway obstruction, management of AAT deficiency associated liver disease, use in patients who have undergone a liver transplant and those who are heterozygous for the gene mutation.[5]

Limitations

Overall the quality of the literature included in the SRs and guidelines had a high risk of bias. Since AAT deficiency is an uncommon disease with a potentially long clinical course, using traditional trial such as RCTs to establish effectiveness may be difficult.[4,19] As such, considering other forms of evidence such as observational study designs including registry or cohort studies, using adaptive trial designs and surrogate outcomes have been

suggested as ways to study uncommon diseases.[19] These study designs come with challenges and potential for bias. Conflicting evidence exists between RCT and observational studies with respect to the rate of decline in FEV1 with AAT augmentation therapy. This was also found in the previous CADTH report.[9] The role of measuring CT lung density as a surrogate measure is controversial in the literature.[1,14] Some of the criticism of this outcome measure has been related to variation in skill of interpretation, availability of different methods of measurement, and variable correlation between lung density and severity of emphysema.[1] Minimal clinical important difference in CT density has not been determined.[12] It is possible that studies published to date have insufficient follow-up to see the effect of an intervention in a disease with potentially slow clinical progression.[4] Several authors and organizations were listed as having received funding from manufacturers of AAT augmentation therapy. This may also introduce a source of bias. The lack of pharmacoeconomic analysis makes cost effectiveness of AAT augmentation therapy challenging to determine.

Generalizing the CTS guidelines to the Canadian population is reasonable, as this was the intended patient population for guideline application. The findings of the SRs may not be generalizable to the Canadian population as they were conducted in Europe, as were two of the included RCTs, and the prevalence of AAT deficiency may be different in this region.

Conclusions and Implications for Decision or Policy Making

Two SRs,[12,13] that included the same three RCTs, evaluated the clinical effectiveness of AAT augmentation therapy for the treatment of adults with AAT deficiency. One of the RCTs was the RAPID trial.[17] This trial was published in 2015 was not included in the previous CADTH report published in 2010.[9] The two other RCTs were included in the 2010 CADTH report.[9] The two SRs included in this report found conflicting evidence of the prevention in decline of FEV1 with the use of AAT augmentation therapy.[12,13] RCT data did not find that AAT augmentation therapy slowed decline in FEV1; however, observational data did find that AAT augmentation therapy was associated with a significant reduction in the rate of decline in FEV1. These findings are consistent with what was reported in one of the included guidelines.[15] Meta-analysis of three RCTs did find that AAT augmentation therapy was associated with a significantly slower reduction in CT lung density. The clinical utility of this outcome measure has been criticized in the literature.[1,12] Four evidence based guidelines suggest that as part of the treatment of AAT deficiency, AAT augmentation therapy could be considered in previous or never smokers with evidence of air flow obstruction who are receiving conventional pharmacologic and non-pharmacologic management. The degree of airflow flow obstruction in which AAT augmentation therapy is recommended varied across guidelines from an FEV1<65%,[5] FEV1<80%,[14] FEV1 25% to 80%,[1] and FEV1 35% to 60%.[15] These recommendations are based on observational evidence of benefit on lung function (rate of FEV1 decline) and CT scan lung density.[1,15]

What remains unknown is the optimal outcome measure to determine clinical effectiveness of AAT augmentation therapy based on the natural history and pathophysiology of AAT deficiency. In April 2011, the Ontario Committee to Evaluate Drugs (CED) issued a funding decision for the use of AAT augmentation therapy, specifically Prolastin, in individuals with AAT deficiency.[20] CED recommended against funding Prolastin as it had not demonstrated a meaningful clinical benefit and value for money.[20] At the time of the recommendation, CED reported that the annual cost of Prolastin was approximately $90,000 per patient.[20] The CED report did not include a pharmacoeconomic analysis as part of the report or recommendations. There is an ongoing study (SPARTA) designed to evaluate the effect of

two different doses of Prolastin-C on lung tissue loss measured by CT scan in adults with AAT deficiency.[21] This trial is expected to be completed in 2021.[13] Based on available evidence, the clinical benefit of AAT augmentation therapy is limited to reduction in CT scan lung density and reduced decline in FEV1 found only in observational studies and not replicated in RCT data. The level of available evidence and lack of cost effectiveness data on products available in Canada creates a challenge with respect to implications for policy decision making.

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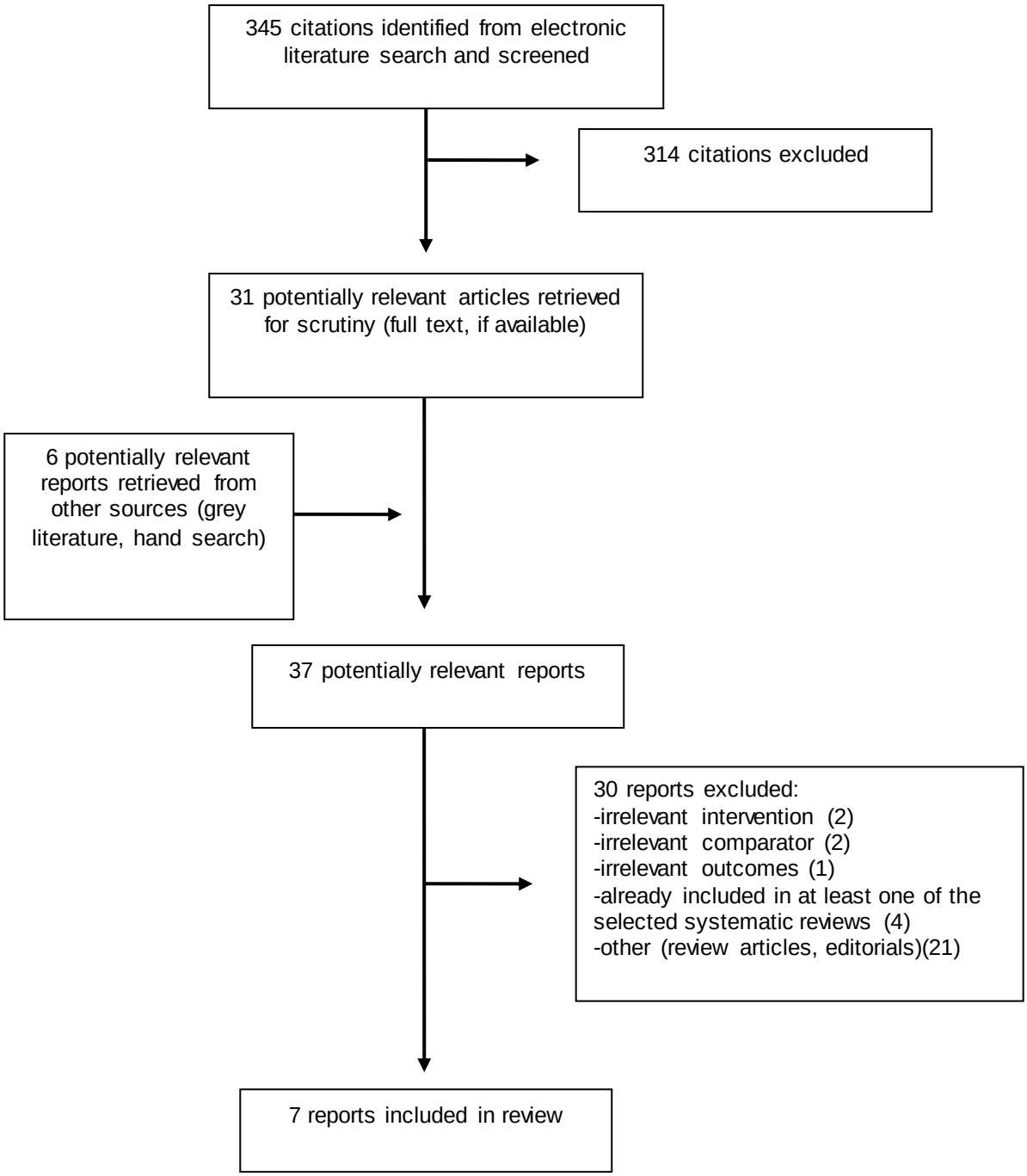
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, County	Types and numbers of primary studies included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Edgar,[12] 2017, UK	52 included studies (n=5632 participants) 26 trials evaluating AAT augmentation therapy 3 RCT (n=320 participants) 6 controlled observational studies (n=2610 participants) 12 uncontrolled observational studies (n=2526 participants)	RCTs: Mean FEV1: Intervention: 46.3 to 50 Control: 46.2 to 47.2 Mean Age: Intervention: 53.8 to 54.7 years Control: 52.4 to 55.3 years % Male: Intervention: 51.6 to 65.8 Control: 41.0 to 57.5	Prolastin Prolastin-C Aralast Zemaira Trypsone Respitin Glassia Dosing ranged from weekly to monthly Most 60mg/kg/week	Placebo No augmentation therapy	Lung Density (CT scan) FEV1 % DLCO Quality of Life Exacerbation Rate Mortality Follow-up: 4 weeks to 7 years
Gotzsche,[13] 2016, Denmark	3 included studies (n=330) All included studies were RCT	Previous or never smokers homozygous for deficiency Severe AAT deficiency (serum levels <11umol) Moderate emphysema FEV1=30 to 80%	alpha-1 antitrypsin infusion 250mg/kg every 4 weeks or 60mg/kg weekly	Placebo	Mortality Exacerbations Lung infections Hospital admissions Quality of Life DLCO FEV1 Lung density measured by CT scan Follow-up: 2 to 3 years

AAT = alpha-1 antitrypsin; DLCO = diffusing capacity of the lungs for carbon monoxide; FEV1 = forced expiratory volume in 1 second; RCT = Randomized Controlled Trial; UK = United Kingdom

Table 3: Characteristics of Included Guidelines

Organization, Publication Year, County	Guideline Methodology	Target Population Characteristics	Intervention(s)	Comparator(s)	Guideline Outcomes
GOLD Guidelines,[15] 2017, Worldwide	SR	AAT deficiency	AAT augmentation therapy	None	NR
COPD Foundation,[5] 2016, USA	SR	AAT deficiency	AAT augmentation therapy	None	NR
SEPAR / REDAAT,[14] 2015, Spain	SR Followed methodology of GRADE, regulations for writing SEPAR guidelines, American College of Chest Physicians Task Force criteria (amended by the CTS COPD clinical assembly Alpha-1 antitrypsin deficiency expert working group)	AAT deficiency in patients with COPD (including patients with severe AAT deficiency associated COPD)	AAT augmentation therapy	None	NR
CTS,[1] 2012, Canada	AGREE II SR Recommendations based on GRADE methodology	AAT Deficiency FEV1/FVC<0.7 AAT levels <11µmol/L	AAT augmentation therapy	None	Decreased exacerbations Improved QoL / health status Reduction in dyspnea Improved exercise capacity Improved activity Decreased health care use Reduction in mortality reduction in rate of lung function decline Stabilization of CT scan lung density

AAT = Alpha-1 Antitrypsin; AGREE = Appraisal of Guidelines Research and Evaluation; CT = computed tomography; CTS = Canadian Thoracic Society; FEV1 = Forced Expiratory Volume in 1 second; FVC = Forced Vital Capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GRADE = Grading of Recommendation Assessment, Development and Evaluation; NR = Not Reported; QoL = Quality of Life; REDAAT = Spanish Registry of Patients with alpha-1 antitrypsin deficiency; SEPAR = Spanish Society of Pulmonology and Thoracic Surgery; SR = Systematic Review; USA = United States of America

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[10]

Strengths	Limitations
Edgar,[12] 2017	
• Authors reported an *a priori* study design • Study selection was completed independently by two reviewers • A comprehensive literature search was performed and authors were contacted for missing data. References lists of included studies were reviewed • Grey literature was searched including clinical trial registries, conference proceedings and abstracts • A list of included studies was provided • Characteristics of included studies were reported • Scientific quality of included studies was assessed and documented • Statistical methods used to combine the findings of individual studies were appropriate	• Data extraction and risk of bias was completed by one reviewer and checked by a second • A list of excluded studies was not reported • Quality of the included studies was not discussed when formulating conclusions • Publication bias was not assessed • Two of the authors of the SR reported receiving grant support from Alpha-1 Foundation • Conflicts of interest for the included studies were not reported
Gotzsche,[13] 2016	
• Authors reported an *a priori* study design • Study selection was completed independently by two reviewers • Outcome data was extracted independently by two reviewers • A comprehensive literature search was performed (two databases were searched) and authors were contacted for missing data • Grey literature was searched including clinical trial registries • A list of included studies was provided • Scientific quality of included studies was assessed (by two reviewers independently) and documented • Quality of the included studies was considered when formulation conclusions • Statistical methods used to combine the findings of individual studies were appropriate • Authors reported a plan to assess for publication bias, however, were unable as too few studies were included • Authors of the systematic review reported that they had no conflicts of interest. Conflict of interested of the included studies was considered	• Descriptive data was extracted by one reviewer and checked by a second • Authors limited searches to randomized trials and do not report whether reference lists were searched • A list of excluded studies was not reported • Characteristics of included studies were not fully reported

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Strengths	Limitations
GOLD,[15] 2017	
• Overall objectives and health questions of the guideline are specifically described • The population to whom the guideline is meant to apply is specifically described • Target users of the guidelines are defined (clinicians)) • Evidence was obtained through systematic review methods • Strength and limitations of the included evidence was discussed but not assessed using a standardized quality appraisal or risk of bias tool • Methods for formulating the recommendations are clearly described • An explicit link between guideline recommendations and evidence is made • Guidelines were reviewed by external experts • A procedure for guideline updates was clearly described • Guideline recommendations are clearly described and easily identifiable • Guideline describes facilitators and barriers to its application (cost and lack of high quality RCT evaluating spirometry) • Guidelines describe methods that have been developed to assist with implementation into practice (Dissemination Committee) and annual guideline revision • The guidelines state that they incorporate values or preferences of patients • Alternative management options are described in the guidelines	• The guideline development group is mainly comprised of physicians, although multidisciplinary consultation is obtained • Only published literature is included • Criteria for selecting evidence was unclear and left to the discretion of members of the scientific committee • Resource implication for incorporating guidelines into practice have not been clearly described • Funding for guideline development is not reported
COPD Foundation,[b] 2016	
• Overall objectives and health questions of the guideline are specifically described • The population to whom the guideline is meant to apply is specifically described • Target users of the guidelines are defined (clinicians) • Evidence was obtained through systematic review methods • Methods for formulating the recommendations are clearly described • The link between evidence and recommendations is often reported but not consistently • Guideline recommendations are clearly described and easily identifiable • Guideline describes some facilitators and barriers to its application • Resource implication (mainly cost) for incorporating guidelines into practice have been considered	• Guideline development group is mainly limited to physicians • The guidelines do not discuss the values or preferences of patients (although, support for the guideline writing committee was provided a patient organization, the Alpha-1 Foundation) • Criteria for selecting evidence was unclear • Limitations and potential bias of the evidence is not clearly discussed • The potential side effects or risks of the intervention are not discussed • The link between evidence and recommendations is inconsistent • An external review process is not described • A procedure for future guideline updates was not described • Alternative management options are not clearly described in the guidelines • Advice or tools for translation of guidelines into practice are not provided • Funding support of the guideline writing committee was provided by the patient organization, the Alpha-1 Foundation. The guideline writers also received funding from pharmaceutical companies, some of whom

Strengths	Limitations
	manufacture AAT augmentation therapy
SEPAR / REDAAT,[14] 2015	
• Overall guideline objectives are specifically described • The population to whom the guideline is meant to apply is specifically described • The guidelines are written in collaboration with the Spanish registry of patients advisory committee, however, it is unclear whether patient preferences are taken into consideration when formulating the guidelines • Evidence was obtained through systematic review methods • Strength and limitations of the evidence are described • Methods for formulating recommendations are clearly described • An explicit link between guideline recommendations and evidence is made • Guideline recommendations are clearly described and easily identifiable • Resource implication (mainly cost) for incorporating guidelines into practice have been considered	• Health questions covered by the guidelines are not clearly defined • It is unclear what professional group the guideline development group belongs • The target users for the guidelines are not clearly defined • Criteria for selecting evidence was not clearly described • Risks associated with augmentation therapy were not clearly considered when formulating recommendations • It is unclear whether the guidelines were externally peer reviewed • A procedure for future guideline updates was not described • Alternative management options are not clearly described in the guidelines • Facilitators and barriers to the application of the guidelines are not clearly described • Advice or tools for translation of guidelines into practice are not provided • Authors did not receive funding for the guidelines. Authors have received funding from various pharmaceutical companies, including a manufacturer of AAT augmentation therapy
CTS,[1] 2012	
• Overall objectives and health questions of the guideline are specifically described • The population to whom the guideline is meant to apply is specifically described • The guideline development group is multidisciplinary • Target users of the guidelines are defined (specialist and generalist physicians, nurses, health care administrators and systems) • Evidence was obtained through systematic review methods • Strength and limitations of the included evidence was discussed but not assessed using a standardized quality appraisal or risk of bias tool • Methods for formulating the recommendations are clearly described and consider the health benefits, side effects, and risks • An explicit link between guideline recommendations and evidence is made • Guidelines were reviewed by external experts • A procedure for guideline updates was clearly described • Guideline recommendations are clearly described and easily identifiable • Guideline describes facilitators and barriers to its application (cost and lack of high quality RCT with long term follow-up) • Guidelines describe tools that have been developed to assist with implementation into practice • Funding is through both grants and pharmaceutical companies which are facilitated centrally. Funders had no	• The guidelines do not discuss the values or preferences of patients • Criteria for selecting evidence was unclear • Alternative management options are not clearly described in the guidelines • Resource implication for incorporating guidelines into practice have not been clearly described

Strengths	Limitations
direct role in guideline development. Conflict of interest of guideline working group are reported and updated regularly.	

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Edgar,[12] 2017	
Meta-Analysis of RCT (AAT augmentation therapy vs placebo) **Outcome** / **# studies (n=participants)** / **Mean Difference (95%CI); P-value** **Lung Density (mean annual change)** / 3 (n=300) / 0.79 (0.29, 1.29) P=0.002 **Mean FEV1% predicted decline** / 2 (n=236) / -0.56 (-1.41, 0.29) P=0.20 **DLCO** / 3 (n=313) / -0.11 (-0.33, 0.11) P=0.34 **Annual patient reported exacerbation episodes** / 3 (n=257) / 0.29 (0.04, 0.54) P=0.02 **Health Status (SGRQ)** / 2 (n=254) / -0.83 (-3.55, 1.89) P=0.55 **Mortality (1 RCT):** Intervention = 1 Placebo = 3 **Observational Controlled Studies** *Mortality* Overall Mortality (1 study, n=1129): 18.1% (n=204) Higher mortality (P<0.001) in participants (FEV1 <50%) who "never" received augmentation therapy compared to "sometimes" or "always" *FEV1 Decline* FEV1 decline in patients with mean FEV1 values 35% to 49% (1 study, n=NR): Receiving augmentation therapy -73.7 +/- 6.8 vs. -93.2 +/- 8.9; P=0.03 FEV1 annual decline (1 study, n=NR) Treatment vs. placebo: -53 mL/year (48, 58) vs. -75 mL/year (63, 87); P=0.02 FEV1 Decline (1 study, n=NR) Pre vs. Post augmentation therapy: -34.3mL/year +/-29.7 vs. 49.2mL/year +/-60.8; P=0.019 FEV1 Decline (1 study, n=164) Untreated vs. treated: 10.61mL/year +/-21.4 vs. -36.96 mL/year +/- 12.1; P=0.05 FEV1 Decline based on subgroup (3 studies)	Good evidence exists that the use of intravenous augmentation therapy slows the decline in emphysema as measured by CT density. The findings of the systematic review demonstrate that augmentation therapy is the main disease specific intervention. Given the cost of augmentation therapy, an economic evaluation is needed.

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>FEV1<30%: no benefit
FEV1>65% (2 studies):
-122.5mL/year +/- 108.4 vs. -48.9 mL/year +/-54.9; P=0.045
-108.7mL/year +/- 17.3 vs. -29.2mL/year +/- 15.29; P=0.0006

Exacerbations
Pre vs. Post augmentation therapy (1 study, n=127)
1.2+/-1.6 vs. 1.0+/-2.2; P<0.01

Observational Uncontrolled Studies
Decline in FEV1 (1 registry study, n=287):
FEV1<30%: -35.6+/-21.3 mL vs. FEV1 30-65%: -64.0+/-26.4mL, P=0.0008</td><td></td></tr>
<tr><td colspan="2">Gotzsche,[13] 2016</td></tr>
<tr><td>AAT Augmentation Therapy vs. Placebo
<table>
<tr><th>Outcome</th><th># studies (n=participants)</th><th>SMD (95%CI); P-value</th></tr>
<tr><td>Change FEV1 (mL or %)</td><td>3 (n=283)</td><td>-0.19 (-0.42, 0.05); P=0.12</td></tr>
<tr><td>Change DLCO</td><td>3 (n=283)</td><td>-0.11 (-0.35, 0.12); P=0.34</td></tr>
<tr><td>Change CT Lung Density (g/L)</td><td>3 (n=273)</td><td>0.86 (0.31, 1.42); P=0.002</td></tr>
</table>
Overall Mortality (1 study, n=180):
AAT=1 vs. Placebo=3, P=NR

Mean Annual Exacerbation Rate (2 studies, n=NR)
AAT 2.55 (SD: 2.14) vs. Placebo 2.19 (SD: 2.14); P=NR
AAT 1.70 (95%CI: 1.51, 1.89) vs. Placebo 1.42 (95%CI: 1.23, 1.61), RR=1.26 (95%CI: 0.92, 1.74)

Quality of Life (SGRQ) (2 studies, n=NR)
AAT 1.5 vs. Placebo 2.4; P=0.70
AAT -1.4 vs. Placebo 2; P=NR

Lung infections=NR
Hospital admissions=NR</td><td>Lack of data prevented the authors from drawing conclusions regarding the effect of AAT augmentation therapy on mortality, exacerbations, lung function, hospital admission and quality of life. Authors also reported that uncertainty exists regarding possible harms of augmentation therapy. The opinion of the authors is that augmentation therapy not be recommended.</td></tr>
<tr><td colspan="2">GOLD,[12] 2017</td></tr>
<tr><td>Observational studies have demonstrated that AAT augmentation therapy results a reduction in progression in spirometry compared to no treatment. These effects are most pronounced in individuals with an FEV1 between 35% and 49% predicted.
Previous or never smokers with AAT deficiency and an FEV1 35-60% are most suitable for AAT augmentation therapy (Evidence level B)

Evidence level B = RCTs with important limitations or limited body of evidence</td><td>IV AAT augmentation therapy may slow the progression of emphysema.</td></tr>
<tr><td colspan="2">COPD Foundation,[5] 2016</td></tr>
</table>

Main Study Findings	Author's Conclusion

Recommendations for IV augmentation therapy use in individuals with AAT Deficiency

Degree of airflow obstruction	Recommendation	Strength
FEV1<30%	Recommended	Weak recommendation Low quality evidence
FEV1 30% to 65%	Recommended	Strong recommendation High quality evidence
FEV1>65%	Individual discussion regarding potential benefits of reducing lung function decline, potential cost and lack of evidence for such benefit	Strong recommendation Low quality evidence
NA	IV augmentation therapy is recommended for individuals with necrotizing panniculitis	Strong recommendation Low quality evidence

Recommendations against IV augmentation therapy in individuals with AAT Deficiency

Recommendation	Strength
not recommended for AAT deficient individuals who continue to smoke	Weak recommendation Low quality evidence
not recommended in individuals with AAT deficiency and bronchiectasis without evidence of airway obstruction	Weak recommendation Low quality evidence
not recommended for management of liver disease	Strong recommendation Low quality evidence
not recommended for individuals who have undergone a liver transplant	Strong recommendation High quality evidence
not recommended for heterozygote individuals	Strong recommendation Low quality evidence

Recent evidence strongly supports the use of AAT augmentation therapy in appropriate individuals with lung disease secondary to AAT deficiency. Gaps in evidence still remain and therefore expert opinion and observation played a prominent role in development of the recommendations in these guidelines.

SEPAR / REDAAT,[14] 2015

Criteria to IV AAT Augmentation Therapy:

- Age ≥18 years
- AAT deficiency (demonstrated by serum concentrations ≤50mg/dl)
- Never smokers or previous smokers (with at least 6 months of abstinence)
- Evidence of pulmonary emphysema demonstrated by

AAT deficiency is a rare genetic condition which most commonly manifests as pulmonary emphysema. There is sufficient evidence to recommend the use of AAT replacement therapy in certain clinical circumstances.

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td>pulmonary function tests or CT scan
• COPD with FEV1<80% predicted AND receiving optimal pharmacological and non-pharmacological treatment
• No evidence of IgA deficiency
• Prepared to receive regular treatments at a day hospital

(all criteria must be met)
Recommendation is based on moderate quality evidence</td><td></td></tr>
<tr><td colspan="2">CTS,[4] 2012</td></tr>
<tr><td>Recommendations based on 6 studies
<table>
<tr><th>Outcome</th><th>Effectiveness of AAT Augmentation Therapy</th><th>Quality of Evidence</th></tr>
<tr><td>Exacerbations</td><td>No evidence of benefit</td><td>Grade B</td></tr>
<tr><td>Quality of Life</td><td>No evidence of benefit</td><td>Grade B</td></tr>
<tr><td>Dyspnea</td><td>NR</td><td>NA</td></tr>
<tr><td>Exercise performance</td><td>NR</td><td>NA</td></tr>
<tr><td>Activity Limitation</td><td>NR</td><td>NA</td></tr>
<tr><td>Health care use</td><td>NR</td><td>NA</td></tr>
<tr><td>Mortality</td><td>Benefit</td><td>Grade C</td></tr>
<tr><td>Lung Function (Rate of FEV1 decline)</td><td>Benefit</td><td>Grade C</td></tr>
<tr><td>CT scan lung density</td><td>Benefit</td><td>Grade C</td></tr>
</table>
Grade B recommendation = randomized trials with limitations including inconsistent results or major methodological weaknesses

Grade C recommendation = Observational studies and generalization of randomized trials to a different group of patients</td><td>The CTS recommends that AAT augmentation therapy may be considered in non-smokers or previous smokers with AAT deficiency (level ≤11µmol/L) with COPD (FEV1 25% to 80% predicted) who are receiving optimal pharmacological and non-pharmacological management based on benefits seen in CT scan lung density (Grade 2B recommendation) and mortality (Grade 2C recommendation)

Grade 2B recommendation = Weak recommendation (desirable effects closely balanced with undesirable effects) based on randomized trials with limitations

Grade 2C recommendation = Weak recommendation (desirable effects closely balanced with undesirable effects) based on observational studies or generalization of randomized trials to a different group of patients</td></tr>
</table>

AAT = Alpha-1 Antitrypsin; COPD = Chronic Obstructive Pulmonary Disease; CT = computed tomography; CTS = Canadian Thoracic Society; DLCO = diffusing capacity of the lungs for carbon monoxide; FEV1 = forced expiratory volume in 1 second; IV = intravenous; NA = not applicable; NR = Not Reported; RCT = Randomized Controlled Trial; SMD = Standard Mean Difference; SRGQ = St Georges Respiratory Questionnaire

Appendix 5: Additional References of Potential Interest

Pharmacoenconomic Analysis of AAT Augmentation therapy not approved in Canada

Sclar DA, Evans MA, Robison LM, Skaer TL. α1-Proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to α1-antitrypsin deficiency: Number and costs of years of life gained. Clin Drug Investig. 2012;

Non-evidence based Guidelines

Chorostowska-Wynimko J, Bakuła A, Kulus M, Kuca P, Niżankowska-Mogilnicka E, Sanak M, et al. Standards for diagnosis and care of patients with inherited alpha-1 antitrypsin deficiency Recommendations of the Polish Respiratory Society, Polish Society of Pediatric Pulmonology and Polish Society of Pediatric Gastroenterology. Pneumonol Alergol Pol. 2016;